IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, **ADRIAN PAUL BROWN, M.A., M.I.L., M.I.T.I.**, declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 5 Gilbert Road, London, SE11 4NZ.

2. That I am well acquainted with the French and English languages.

3. That the attached is a true translation into the English language of the Request and Specification as filed of International Patent Application No. PCT/FR03/00179.

4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 7th DAY OF APRIL 2004

a. P. Brown

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ORODISPERSIBLE PHARMACEUTICAL COMPOSITION OF PIRIBEDIL

The present invention relates to a solid orodispersible pharmaceutical form for the administration of piribedil or pharmaceutically acceptable salts thereof by the oral route.

Piribedil is a dopamine agonist which stimulates dopamine receptors and the cerebral and peripheral dopaminergic pathways.

Piribedil has hitherto been administered by the oral route in the form of prolonged-release tablets to be swallowed with half a glass of water. The said piribedil tablets are useful in the treatment of chronic pathological cognitive and neurosensory deficit in the elderly patient, in the ancillary treatment of intermittent claudication in chronic occlusive arteriopathies in the lower limbs and in the treatment of Parkinson's disease.

Piribedil may also be administered by the injectable route in order to improve the painful manifestations of arteriopathies in ischaemic attack, sometimes in association with surgical treatment.

Pharmacokinetic studies in humans have shown that the bioavailability of piribedil by the oral route is low in relation to the parenteral route and is subject to considerable variation within one and the same individual and from one individual to another.

The currently marketed form of piribedil is a prolonged-release form allowing gradual absorption and release of the active ingredient. Kinetic studies in humans have shown that, for the 50 mg dose, therapeutic levels are spread out over a period lasting more than 24 hours.

However, especially for the treatment of Parkinson's disease, the moderate bioavailability of piribedil and the inter- and intra-individual variations in concentration have resulted in the search for a new formulation allowing those problems to be solved. In addition, it was especially desirable for such Parkinson's patients that a rapid-action form be made

available to medical staff in order to treat the very frequent acute attacks in those patients and for the rapid alleviation of akinesia.

The pharmaceutical compositions of the present invention make it possible not only to solve the known problems of the prolonged-release form but also to offer a superior medical service which especially allows the quality of life of patients to be improved.

The orodispersible pharmaceutical composition of piribedil has the advantage that elevated plasma levels of active ingredient are obtained rapidly and that, from the metabolic point of view, the significant metabolisation of the active ingredient due to the hepatic first-pass effect is avoided and, from the clinical point of view, efficacy in acute episodes of Parkinson's disease is improved.

The orodispersible pharmaceutical composition according to the invention has the particular characteristic of requiring neither water nor chewing in the course of its administration. It disintegrates very rapidly in the mouth, preferably in less than three minutes and even more preferably in less than one minute.

Many rapid-dissolution forms are described in the prior art. In general, it is common to the previously described technologies that they use a disintegrating agent such as Kollidon® CL (crosslinked polyvinylpyrrolidone), EXPLOTAB® (carboxymethyl starch) and AC DISOL® (crosslinked sodium carboxymethylcellulose).

That disintegrating agent is indispensable to the formulation of the orodispersible tablets and has to be used in conjunction with a direct-compression excipient. The difficulties encountered in the manufacture of such tablets reside in the fact that it is very difficult to obtain tablets having physical characteristics that are constant and reproducible and compatible with the customary handling requirements of tablets.

However, the customarily used mixtures result in tablets of very substantial hardness which is completely unsuitable for rapid disintegration in the oral cavity.

Other orodispersible forms can be produced by using lyophilisation, resulting in very porous solid forms called "oral lyophilisates". Those forms require the use of a highly specific and complicated industrial process which is lengthy to carry out, yielding a medicament form which has a high cost price.

The present invention enables those problems to be solved. It relates to a solid orodispersible form of piribedil comprising a single excipient of natural origin which allows rapid disintegration and which has a neutral flavour and agreeable texture. The said excipient acts both as binder and as disintegrant. It allows a simple piribedil formulation to be obtained, having excellent suitability for direct compression, resulting in tablets of low friability and of a hardness that is compatible with customary handling methods.

More specifically, the invention relates to a solid orodispersible pharmaceutical composition of piribedil or pharmaceutically acceptable salts thereof, characterised in that it comprises :

- piribedil or a pharmaceutically acceptable salt thereof,
- and granules consisting of co-dried lactose and starch.

The composition according to the invention may also comprise, for reasons of manufacture, one or more lubricants and a flow agent, as well as flavourings, colourings and sweetening agents as conventionally used.

The invention relates also to the use of granules consisting of co-dried lactose and starch in the manufacture of solid orodispersible pharmaceutical compositions of piribedil.

Because certain Parkinson's patients suffer from hyposalivation (dry mouth), it is also possible for an acid such as citric acid to be added to the pharmaceutical compositions according to the invention in order to promote salivation in those patients.

The term "orodispersible" is understood to refer to solid pharmaceutical compositions which disintegrate in the oral cavity in less than 3 minutes, preferably less than one minute.

The said granules present in the solid pharmaceutical compositions according to the invention correspond to the compositions described in Patent Application EP 00/402159.8. Those granules are characterised by a spherical structure and an advantageous compressibility and are marketed under the name STARLAC®.

The disintegrating properties of the said granules are known for tablets placed in large volumes of stirred liquids. It is especially surprising that, when used in the manufacture of orodispersible forms, the said granules should give especially satisfactory results in terms of disintegration in the mouth, for two reasons.

The first reason is based on the finding that the least water-soluble excipients are the most suitable for the formulation of orodispersible tablets (dissolution, in bringing about an increase in the viscosity of water, slows down its penetration into the tablets) and yet the said granules contain a large amount of highly water-soluble lactose. Moreover, the starch contained in the said granules is not a "super-disintegrant" agent as used and described in the orodispersible forms of the prior art.

The second is based on the finding that the disintegrant properties of an excipient (used in a tablet), when determined in water using conventional methods, cannot be extrapolated to the behaviour of the same tablet *in vivo*, in saliva. Disintegration rates in water are measured (in accordance with the European Pharmacopoeia) in an amount of water that is sufficiently large not to reach saturation level in terms of dissolution, whereas *in vivo*, by virtue of the small volume of saliva, the excipients are at saturation level. Furthermore, the stirring to which the tablets are subjected in the customary test does not reflect disintegration in the mouth. The Applicant accordingly found, during comparative tests, that certain excipients which are known as good disintegrants are not suitable for the preparation of orodispersible forms. Conversely, certain excipients that exhibit average disintegration in water may exhibit advantageous properties *in vivo*.

The Applicant then found, surprisingly, that the said granules rendered the tablets highly suitable for disintegration in the mouth, that being the case over a wide tablet hardness range, whilst maintaining a low level of friability, which is especially remarkable. Most

orodispersible forms of the prior art which disintegrate rapidly in the mouth are highly friable, which is reflected by the need to use a specific packaging and the risk of the tablet disintegrating as soon as it is handled and taken out of its pack.

It is especially remarkable that the above-mentioned criteria of orodispersibility and low friability are maintained over a wide tablet hardness range, that is to say for tablets having a hardness of from 15 to 30 Newtons.

The pharmaceutical compositions according to the invention are preferably characterised in that they comprise, in relation to the total weight of the tablet:

- from 5 % to 50 % by weight of piribedil or a pharmaceutically acceptable salt thereof, even more preferably from 10 % to 20 %,
- from 50 % to 95 % by weight of STARLAC®.

They may optionally comprise from 0.1 % to 3 % by weight of lubricating agents such as magnesium stearate or sodium stearyl fumarate, preferably from 0.5 % to 1.5 %, and from 0.1 % to 3 % by weight of a flow agent such as colloidal silica, preferably from 0.5 % to 1.5 %.

When an acid is added to the pharmaceutical composition according to the invention, the amount thereof will preferably be from 0.1 to 3 % by weight.

The following Examples illustrate the invention without limiting it in any way :

Orodispersible piribedil tablets

EXAMPLE 1 :

Formulation : Finished tablet of 100 mg

Constituents	*Amount (mg)*
Piribedil*	10
Starlac®	89
Magnesium stearate	0.5
Anhydrous colloidal silica	0.5

(*) in the form of the micronised base

EXAMPLE 2 :

Formulation : Finished tablet of 100 g

Constituents	*Amount (mg)*	
	F1	F2
Piribedil*	10	10
Starlac®	87	85.5
Citric acid	1.5	3
Lemon flavouring	0.5	0.5
Magnesium stearate	0.5	0.5
Anhydrous colloidal silica	0.5	0.5

(*)in the form of the micronised base

The tablets are prepared by mixing the constituents, followed by direct compression. The hardness of the tablets of Examples 1 and 2 is about 20 Newtons.

In order to determine the disintegration time in the mouth, the orodispersible piribedil tablets described in Examples 1 and 2 were placed under the tongue in order to promote the systemic passage of piribedil by the sublingual route and to avoid as far as possible the hepatic first-pass effect.

In these tests it was found that, for each of the formulations tested, the disintegration time in the mouth was less than 1 minute.